GNR Transmitted by Animals

Introduction

The organisms in this lesson are **Gram-negative rods** and **facultative intracellular bacteria**. This means they can grow inside eukaryotic cells, necessitating prolonged antibiotics to get the bugs hiding in infected cells. These organisms are also **zoonotic**—carried by or transmitted by animals. These organisms are also **incredibly virulent**, such that diagnosis should not involve culturing of the bug—the culture you grow is too likely to infect another person. Because they are intracellular, the immune response is restricted to cell-mediated immunity—killing the macrophages hosting the bacteria. This allows for a **PPD-like skin test** to assess exposure to the organism, aiding in diagnosis.

This lesson is forced by our taxonomy. These are all Gram-negative organisms and happen to be associated with animals. We do not have an "all Gram-stain zoonotic" lesson, simply because we did not organize the module that way. Should you construct such a table to memorize from (we discourage this), make sure you include the organism's Gram stain and shape, not just the disease and the animal vector.

Finally, the incidence of these infections is critically low. Except for *Pasteurella multocida* (the bacteria of common cat, dog, and human bites), each bacterium discussed in this lesson has an incidence of 100 cases per year (or fewer) in the US. They remain commonly board-tested organisms, but are super-low-yield for clinical practice. If you see microbiology as daunting, maybe leave these off your study list. If you will practice medicine in endemic areas, you will be informed of the need to be on alert for the disease. If you will not, you need only the information needed to pass the Board Exam.

Yersinia pestis (aka "The Bubonic Plague")

Yersinia pestis causes the plague. It is a Gram-negative rod and is a facultative intracellular bacterium. Being facultatively intracellular means that the bacteria must be small. It is carried on rats and transmitted to humans by fleas. Some plague remains in the United States, harbored by ferrets and squirrels in the southwest US.

Virulence. *Yersinia pestis* evades phagocytosis and poisons macrophages. *Yersinia pestis* is a facultative intracellular bacterium capable of replicating in macrophages. *Yersinia pestis* has a **protein capsule** that aids in evading phagocytosis. *Yersinia pestis* also has **plasminogen activator protease**, which degrades complement C3b and C5a, preventing opsonization, again evading phagocytosis. In addition to evasion, the **type 3 secretion system** (T3SS) is a molecular syringe that allows toxins to be infused into macrophages upon contact. Those infused toxins inhibit lysosome fusion with phagosomes, suppress macrophage cytokine release, and can even induce apoptosis. In effect, *Yersinia pestis* avoids being phagocytized. But by the time it finally is, it and its cousins have poisoned the macrophages so that even though phagocytosis has occurred, intracellular killing doesn't happen. And, being facultatively intracellular, the phagocytosed *Yersinia pestis* simply replicates in a subdued host.

History. At least three major pandemics of urban plague, carried by rats, have been recorded. The first probably began in Egypt in the mid-sixth century CE, reaching out around the Mediterranean coast (northern Africa, southern Europe, and the Middle East) and the Arabian Peninsula. The pandemic persisted on and off for around 200 years. The second pandemic was in Europe in the mid-fourteenth century, resulting in the deaths of approximately a third of the population. The third began in China in the mid-nineteenth century, and spread on ships to Africa, Europe, and the Americas. In recent years, fewer than **10 cases per year** have been reported in the United States, and all cases are related to rural wildlife—prairie dogs and ferrets succumb to the plague; humans only happen upon it while carrying animal carcasses or being bit by fleas after large animal populations die. This "of the wild" type of plague is called sylvatic plague, and is impossible to eradicate because it uses mammalian reservoirs in nature.

Urban plague has decimated human civilization multiple times, and was maintained by **rat reservoirs** and transmitted to humans by **rat flea vectors**. Controlling rat populations and better sanitation have essentially eliminated this disease.

Diseases. There are two presentations of *Yersinia pestis*—bubonic plague and pneumonic plague.

Bubonic plague is the cutaneous form of the disease. A flea leaps from its small mammalian host onto a human. The flea bites. The bacteria enter the local tissue where they are phagocytosed by macrophages. The macrophages are poisoned, so the bacteria divide within the macrophage. The macrophage takes its "captive" to the lymph node, intending on getting help. There (because it is an intracellular organism), **cell-mediated immunity** attempts to kill the bacterium and the hapless macrophage with it. This reaction presents with **massively swollen lymphadenopathy** that is **painful** and **hot**. The immune system fails, and the bacteria gain access to the bloodstream. Because fleas have access to the human ankle, and the legs drain to the groin, the disease most often presents with inguinal lymphadenopathy. Boubon is Greek for groin, thus the name of the disease. Once accessed to the bloodstream, they disseminate. Mortality is 75% even with antibiotic treatment. This is called "Black Death" because the overwhelming sepsis causes disseminated intravascular coagulation, clotting extremities, leading to gangrene (which turns black), and then the patient dies (which is death).

The **pneumonic plague** is caused by **inhalation** of organisms from infected individuals and by acts of **bioterrorism**. To be aerosolized, bacteria in the blood of an infected mammal sprays out as it's being butchered (very hard to do by accident). Pulmonary inhalation is highly contagious and rapidly fatal. The macrophages do the same thing as they do in bubonic plague—capture and bring the bacteria to regional lymph nodes. In the lung, that causes **mediastinal lymphadenopathy** and therefore a widened mediastinum on chest X-ray.

Treatment. Prompt treatment with **gentamicin** (aminoglycosides) kills the infection and reduces the mortality. With treatment, bubonic plague's mortality is close to 75% and pneumonic plague 90%. Controlling the vector is the most important intervention, thereby preventing disease in the first place. That means **controlling the fleas**, not the rats. Killing the rats without controlling the fleas just makes really hungry fleas looking to get on humans. Containing the rats and separating them from humans controls the flea vector.

Haven't I seen *Yersinia* somewhere else? Yes. In the lesson on bugs that cause diarrhea, *Yersinia enterocolitica* (entero-colon-itica) was discussed in relation to diarrheal illness. This illustrates our clinical emphasis in microbiology. Do not learn them as *Yersinia*; learn them as *Yersinia pestis*, the bacterium that causes plague, and *Y. enterocolitica*, the one that causes diarrhea.

Francisella tularensis (aka "The Wabbit Plague" or "Tularemia")

Tularemia is called "wabbit plague," because it is associated with rabbits and hunters of rabbits and presents as a milder version of plague. The name "wabbit plague" is intended to make you remember, first, rabbits and their hunters (Elmer Fudd hunting Bugs Bunny); and second, the plague, since the two forms of tularemia that we want you to learn have obvious parallels with *Yersinia pestis*.

Tularemia can be transmitted either by **tick bites** (analogous to plague's rat flea bite) or by **rabbits** (analogous to the rat carrier, except rabbits without the tick can still infect a handler). The **butchering of rabbits** results either in **traumatic implantation** (you cut yourself, and *Francisella*-tinged rabbit blood gets in your skin), or **inhalation** (you breathe deeply around rabbit blood and *Francisella* gets in your lungs). Tick bites cause the skin disease as well.

Ulceroglandular tularemia (the skin disease) looks like bubonic plague. There is a bite of a tick (or traumatic implantation), fever, and the local lymph nodes get red, swollen, and tender (that's the -glandular part). It happens because the bacteria enter the skin and get phagocytosed by macrophages; bacteria prevent fusion of the lysosome, and are brought to the lymph node where cell-mediated immunity causes swelling. However, unlike plague, in tularemia there is also an ulcer at the bite site (that's the ulcero- part). This is the most common presentation of tularemia. Because the bacteria live in the tick feces, prolonged tick attachment (a cycle of feeding, digesting, excreting) is required to inoculate the human with bacteria—simply removing the tick early will avoid infection.

Pneumonic tularemia is caused by inhalation of the bacteria during butchering of the rabbit. The rabbits that can infect humans this way are themselves affected by infection. Humans should not handle diseased animals, if it can be helped, and should wear protective equipment when sacrificing infected rabbits, and butchering rabbits in general.

Other forms exist (typhoidal tularemia if undercooked rabbit meat is ingested, oculoglandular tularemia if the bacteria land in your eye), but limiting your learning to the parallels to *Yersinia pestis* makes this easy to remember. Tularemia is plague-from-rabbits.

Do not culture—the organisms you grow are too dangerous; only 10 organisms are needed to induce disease. Tularemia looks like plague, it sounds like plague (except with an ulcer), and even though it **is not as deadly** as plague, it is treated the same way as plague—aminoglycosides such as **gentamicin**.

Brucella (aka "Undulant Fever" or "Brucellosis")

Brucella species are facultative intracellular Gram-negative rods, like everyone who has come before in this lesson. The species name is dependent on which animal they infect, but you must recognize only "*Brucella*." For completeness, we include the associations: *B. melitensis* infects goats and sheep, and is the one that causes the most severe disease; *B. suis* infects swine; *B. canis* infects dogs; and *B. abortus* infects cattle, the one that causes most disease in the US. The organism has a predilection for infecting organs rich in **erythritol,** a sugar metabolized by *Brucella* strains in preference to glucose. Animal tissues including breast, uterus, placenta, and epididymis are rich in erythritol. Human tissue does not contain any.

Based on its predilection for female reproductive animal tissue, the two ways you are going to see this disease are in **people who handle sheep placentas** and people who **drink unpasteurized milk**. In the US, there are about 100 cases a year.

Bacteria get into a human host. Macrophages phagocytose the bacteria. They are facultatively intracellular, so survive in the macrophage, preventing the fusion of the lysosome. Macrophages bring the bacteria to lymph nodes where cell-mediated killing attempts to kill the bacteria and the organism. Sounds familiar . . . But there is **no lymphadenopathy**. If not treated, the phagocytosed bacteria are carried to the spleen, liver, and bone marrow. The bacteria secrete a protein that induces **granuloma formation** in these organs, the granulomas leading to tissue destruction. This surviving-in-macrophages and granulomas-causing-disease mirrors how *Mycobacterium tuberculosis* affects the lung, the same Th1 response as in pulmonary TB. The patient presents with **undulating fever** that spontaneously relapses and remits, often associated with **arthralgias**, anorexia, and vague inflammatory symptoms unrelated to the location of the bacteria. If suspecting Brucellosis, obtain **serologic antibodies**. While a skin test (brucellergin) is available, a positive test demonstrates only exposure. Cultures can take up to two weeks. Treating prevents long-term sequela and chronic infection. Treatment is with **doxycycline and rifampin**.

Brucellosis is contracted from unpasteurized milk (and sheep placentas) because *Brucella* likes organs that have erythritol. *Pasteurella* (discussed next) is caused by cats. Cats stereotypically drink milk, and the milk given to cats is usually pasteurized milk. So, the visualization of a cat drinking milk can remind you that *Pasteurella* is caused by cats.

Pasteurella multocida (aka "Animal Bite Disease")

Pasteurella is the bacterium of animal bites and is part of the normal flora of domesticated animals—cats and dogs. The **vector is cats** or dogs, but this is **not cat-scratch fever** (that's *Bartonella henselae*); but it can cause a fever, so could be thought of as "cat-bite fever." Cat-bite fever is an OME disease name, and is not something recognized as a colloquialism in microbiology. When a cat bites skin, the wound is deep and skinny, allowing the bacteria to be implanted deep into skin. At the bite site, there may be some redness. Regional lymphadenopathy may follow. If a human or a dog bites skin, the wound is usually larger, not as deep, and easier to clean. If the wound is closed (do not suture close bite wounds) *Pasteurella* grows and symptoms are worse than if you had cleaned it out and left it open. For human, cat, or dog bites, **clean the wound well** and give **amoxicillin/clavulanate** even before evidence of infection occurs. This active treatment is considered prophylaxis. If you don't clean it out and give antibiotics, you could get an ulcer on the skin and regional lymphadenopathy with fever, which sounds similar to ulceroglandular tularemia.

Bites from domestic cats and animals are common. Infections from these bites are common.

This bug is very unlike the previous organisms discussed. This organism is **not facultatively intracellular**.

In fact, *Pasteurella* is more like *Haemophilus influenzae* from a microbiology physiology perspective than *Francisella* or *Yersinia pestis*. However, *Pasteurella* causes a disease that is more in tune with "carried by animals, affects the skin, causes lymphadenopathy" of this lesson, which is why we put it in this lesson—the emphasis being on clinical scenario rather than microbiologic distinction.

Bartonella henselae

Bartonella henselae is the causative organism of bacillary angiomatosis and cat-scratch fever. **Cat-scratch fever** is an indolent, self-resolving condition seen in children. There will be a chronic lymphadenopathy associated with a cat scratch. Antibiotics have not been proven to be effective, and the condition usually resolves. **Bacillary angiomatosis** is a vascular proliferative disorder in immunocompromised patients who grow blood-filled nodules on the skin and bones. Doxycycline or azithromycin is useful for bacillary angiomatosis. Technically, the bacteria live in the cat fleas, and transmission occurs from exposure to flea feces, not from the cat itself—the cat scratches the flea, gets flea feces on its claw, scratches a human, inoculating the bacteria into the person. Cats without fleas cannot cause cat-scratch fever.

Yersinia pestis Bubonic Plague	Capsule (evades phagocytosis) Facultative intracellular (replicates in macrophages, prevents lysosome fusion) Urban plague = Rat reservoir, flea vector; sylvatic plague = southwest US rodents Bubonic plague (lymphadenopathy), gentamicin Pneumonic plague (bioterrorism), death
Francisella tularensis Rabbit Fever	Capsule (evades phagocytosis) Facultative intracellular (replicates in macrophages, prevents lysosome fusion) Rabbit reservoir, rabbit vector, tick vector Super duper low inoculum (10 bacteria to cause infection)—never culture Tularemia—fever, malaise, chills, fatigue (nonspecific viral symptoms), gentamicin Ulceroglandular tularemia—Tularemia + ulcer at bite site, associated lymphadenopathy Pneumonic tularemia—Tularemia + pneumonia that fails to improve
Brucella	Unpasteurized milk (animal breasts) or placenta (animal uterus), erythritol No capsule Facultative intracellular (replicates in macrophages, prevents lysosome fusion) Macrophages bring organism to spleen, liver, bone marrow; macrophages die Organisms are then combatted via granulomas, Th1 immune response Undulating fever with arthralgias
Pasteurella multocida Cat bites	Cat-bite disease (normal flora of domesticated animals, cats have long fangs) Clean out wound really well, do not suture Amoxicillin/clavulanate
Bartonella henselae	Cat-scratch fever—chronic swelling of lymph nodes after cat scratch Bacillary angiomatosis—adults, immunocompromised, blood-filled nodules on skin Cats with fleas scratch fleas, get flea feces on claw, cat scratches human to cause disease

Table 10.1: Summary of Zoo Bugs